

Appl. No. : **10/063,570**
Filed : **May 2, 2002**

DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

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REMARKS

Applicants have cancelled Claim 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide having the amino acid sequence of SEQ ID NO: 64. Claim 1 has also been amended to recite "An isolated antibody." Support for this amendment can be found at paragraph [0246] of the specification. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed February 3, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification

URLs:

The Examiner objected to the specification because it contains embedded hyperlinks. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlink with text that describes the location of the website. The amended text no longer constitutes browser executable code.

Trademarks:

The disclosure also was objected to by the PTO as containing trademarks which were not capitalized and did not include generic terminology. The specification has been amended to include these changes.

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Rejection under 35 U.S.C. §101 – Non-Statutory Subject Matter

The PTO has rejected Claim 1 under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The PTO argues that Claim 1 is drawn to antibodies which are unaltered, naturally occurring articles, and therefore are not articles of “manufacture.”

Applicants have amended Claim 1 to recite “isolated.” In light of the amendment, Applicants request that the PTO withdraw the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-6 as lacking a specific, substantial, and credible utility. The PTO states that the antibodies bind to polypeptides comprising SEQ ID NO:64, but that there is no utility for a polypeptide comprising SEQ ID NO:64. The PTO asserts that “[u]ses such as assaying for binding partners (p. 95), using polypeptides as molecular weight markers (p. 92), and screening for agonists and antagonists of PRO3566 (p. 95-99) are useful only in research to determine the function of the encoded protein itself.” The PTO argues that there is no “specific benefit in currently available form” to be derived from such studies.

The PTO states that “[e]ven though Applicants teach that PRO3566 DNA is ‘more highly expressed’ in normal skin cells and esophageal tumor cells when compared to melanoma tumor cells and normal esophageal cells, respectively ... there is no guidance in the specification as to how high [the] levels are.” The PTO asserts that the asserted utility in diagnosis and treatment of cancers is not substantial. The PTO argues that it is not clear whether the overexpression of PRO3566 is statistically significant and whether such overexpression is correlated to the overexpression of the encoded protein or whether it is due to aneuploidy. According to the PTO, “the specification fails to disclose the biological significance of this overexpression.” Further, according to the PTO, the specification does not teach whether the overexpression is the cause or the result of the tumors, and that the only thing Applicants teach is that the gene was more highly expressed, and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Therefore, the PTO concludes that further research is required to identify or confirm a “real world” utility.

Applicants respectfully disagree.

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Utility – Legal Standard

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that “Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” Further, “[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular

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practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

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[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be a **sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n *vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by

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those in the art. As in *Cross*, Applicants here do not argue that there is “an invariable exact correlation” between gene expression and protein expression. Instead, Applicants’ position detailed below is that a measured change in gene expression in cancer cells establishes a “significant probability” that the expression of the encoded polypeptide in cancer will also be changed based on “a reasonable correlation therebetween.”

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants’ Arguments and the PTO’s Response

Applicants offer below a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly melanoma and esophageal cancer. Applicants’ asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO3566 polypeptide is more highly expressed in normal skin compared to melanoma tumor, and in esophageal tumor compared to normal esophagus;
2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;
3. Given Applicants’ evidence that the level of mRNA for the PRO3566 polypeptide is decreased in melanoma tumors and in normal esophagus tissue compared to normal skin tissue

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and esophageal tumors, respectively, it is likely that the expression of PRO3566 polypeptide in melanoma tumors and normal esophagus tissue is also reduced, and it and antibodies that bind to it are therefore useful as a diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the significance and reliability of the evidence reported in Example 18, and states that these data do not allow a skilled artisan to differentiate amongst expression levels in order to diagnose any disease;

2. The PTO asserts that it is not clear whether the overexpression of PRO3566 is statistically significant or whether such overexpression is correlated to the overexpression of the encoded protein or whether it is due to aneuploidy.

3. The PTO concludes that the data of Example 18 do not necessarily indicate anything significant regarding the claimed antibodies. Therefore, further research needs to be done to use PRO3566 as a cancer diagnostic tool.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 1) which establishes the reliability of the data of Example 18. Knowing the biological significance of the data, or the role of PRO3566 in cancer, is not necessary to use the claimed antibodies as cancer diagnostic tools. Second, whether or not aneuploidy is involved is irrelevant, what is important is that there are different levels of mRNA in normal cells compared to the corresponding tumor cells, which provides a utility for the differentially expressed nucleic acid, the encoded polypeptide and antibodies to the same. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability**, that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

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Applicants have established that the Gene Encoding the PRO3566 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO3566 polypeptide in normal skin and esophageal tumor compared to melanoma tumor and normal esophagus tissue, respectively, is insufficient and unreliable. Applicants also address the PTO's statement doubting the instant utility because aneuploidy may be involved in the differential expression. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed antibodies.

Applicants have submitted herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (Exhibit 1). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

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Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that “[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned.” PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as “opinions” without an adequate explanation of how the declaration fails to rebut the Examiner’s position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to the contrary. Therefore, the PTO should accept Mr. Grimaldi’s opinion with regard to his statement that “any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue” and that the genes of interest “can be used to differentiate tumor from normal.” Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

Applicants fail to see how whether the differential expression reported in Example 18 is due to aneuploidy or not is relevant to the utility of the disclosed nucleic acids, or their corresponding polypeptides and antibodies. Regardless of whether the differential expression of the gene encoding PRO3566 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal skin compared to melanoma tumor, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

The fact that the PRO3566 nucleic acids and polypeptides are differentially expressed confers utility regardless of whether aneuploidy was involved. The Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (See the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially

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expressed polypeptides. (See, e.g., U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 2 and 3.)

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the Grimaldi Declaration submitted as Exhibit 1, establish that there is at least a two-fold difference in PRO3566 cDNA between normal skin and melanoma tumor, and esophageal tumor and normal esophagus tissue. Therefore, it follows that expression levels of the PRO3566 gene can be used to distinguish melanoma tumor tissue from normal skin, and esophageal tumor from normal esophagus tissue. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO3566 polypeptide is also differentially expressed in melanoma tumor tissue and esophageal tumor tissue, and can therefore also be used to distinguish melanoma tumor tissue from normal skin, and esophageal tumor from normal esophagus tissue. This provides utility for the claimed antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that it is not clear whether the overexpression of PRO3566 is correlated to the overexpression of the encoded protein or whether it is due to aneuploidy.

However, as Applicants have stated above, **whether an increase in gene copy number, for example, because of aneuploidy, leads to an increase in gene expression or protein expression is not presently an issue in this application.** The data of Example 18 reflects mRNA data as assessed by examining cDNA created from mRNA. **It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels.** The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO3566 in normal skin and esophageal tumor compared to melanoma tumor and normal esophagus, respectively. It is well-established in the art that changes in the level of mRNA are positively correlated to the changes in the level of protein.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. In fact, the

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working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 4). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 6) and (4th ed. 2002) (submitted herewith

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as Exhibit 7)). Figure 9-2 of Exhibit 6 shows the steps at which eucaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 6 provides that “[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized.” Exhibit 6 at 403 (emphasis added). In addition, the text states that “Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made.” Exhibit 6 at 453 (emphasis added). Thus, as established in Exhibit 6, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 7, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that “a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*” Exhibit 7 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 7 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, “the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes.” Exhibit 7 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, “[f]or most genes transcriptional controls are paramount.” Exhibit 7 at 379 (emphasis added).

Further support for Applicants’ position can be found in the textbook, *Genes VI*, (Benjamin Lewin, *Genes VI* (1997)) (submitted herewith as Exhibit 8) which states “having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.” *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, *World Journal of Surgical Oncology* 2:13, 2004, submitted herewith as Exhibit 9. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed “a high degree of correlation between

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PSCA protein and mRNA expression” Exhibit 9 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that “it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA.” Exhibit 9 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that “PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor.” Exhibit 9 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 10, states the following:

The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO3566 mRNA is expressed at a higher level in normal skin and esophageal tumor compared to melanoma tumor and normal esophagus, respectively, the PRO3566 polypeptide will also be expressed at a higher level in normal skin and esophageal tumor compared to melanoma tumor and normal esophagus, respectively. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed antibodies as cancer diagnostic tools.

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The Claimed Antibodies would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO3566, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the second Grimaldi Declaration, Exhibit 4, Mr. Grimaldi explains that:

However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 11), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 12). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in

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cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed antibodies can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than

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not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly skin cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Specific Utility is defined as utility which is “specific to the subject matter claimed,” in contrast to “a general utility that would be applicable to the broad class of the invention.” M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO3566 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO3566 polypeptide is more highly expressed in normal skin and in esophageal tumor than in melanoma tumor and normal esophagus, respectively. These data are strong evidence that the PRO3566 polypeptide is associated with melanoma and esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO3566 polypeptide with a specific disease. Use of the claimed antibodies as a diagnostic tool for cancer, particularly melanoma and esophageal tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO3566 gene in certain cancers is not significant and reliable; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed antibodies cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO3566 nucleic acids and

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polypeptides in melanoma and esophageal tumors in order to use them and the related antibodies as diagnostic tools for cancer.

Next, Applicants submit that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reasoning or evidence to the contrary. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers, and antibodies that bind to them, have utility as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO3566 gene and polypeptide are differentially expressed in melanoma and esophageal tumors compared to normal skin and esophagus tissue. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a “reasonable” confirmation of a real world context of use. Applicants remind the PTO that:

A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO3566 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

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Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO argues that the claims are indefinite due to the recitation in Claim 6 of “specifically binds.” According to the PTO, it is not clear what the difference is between an antibody that binds and an antibody that specifically binds.

Claim 6 has been cancelled and Claim 1 amended to recite “specifically binds.” In view of the amendment, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

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CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 2, 2005

By: M. T. Morley
Marc T. Morley
Registration No. 52,051
Attorney of Record
Customer No. 30,313
(619) 235-8550

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032305